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Parietal abnormalities are related to avoidance in social anxiety disorder: A study using voxel-based morphometry and manual volumetry

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ABSTRACT

Evidence is accumulating that various mental disorders are related to neural abnormalities in the parietal cortices that are associated with the default mode network (DMN). Participants comprised 67 persons with social anxiety disorder (SAD) and 64 matched healthy controls who underwent structural magnetic resonance imaging (MRI) and a comprehensive clinical assessment. Voxel-based morphometry (VBM) across the entire brain and manual volumetry of the parietal cortices were performed. The results indicate abnormal manually segmented volumes or gray matter (GM) volumes within the precuneus, postcentral gyrus and inferior parietal cortex, as well as in the premotor cortices including the supplementary motor cortex. Significant negative correlations were obtained between parietal, especially precuneus, abnormalities and social avoidance severity, indicating stronger avoidance in SAD participants with smaller volumes or less GM. We conclude that pathological avoidance behaviors in SAD are associated with structural deficits of parietal regions that are associated with the DMN, which has been shown to mediate introspection and reflection upon one's own mental state in healthy humans.

1. Introduction

Social anxiety disorder (SAD) is characterized by extreme and disabling fear and by avoidance of the scrutiny of others (Stein and Stein, 2008). So far, most neuroimaging studies on SAD have focused on the hyperactivation of the amygdala and insula towards social threat, which is considered indicative for an exaggerated fear response in SAD (Etkin and Wager, 2007). However, most studies investigating the neural responses of individuals with SAD towards social threat revealed additional abnormal responses in the medial prefrontal cortex, cingulate cortex and precuneus (Tillfors et al., 2001; Stein et al., 2002; Straube et al., 2004; Amir et al., 2005; Phan et al., 2006; Blair et al., 2008; Goldin et al., 2009; Gimenez et al., 2012).

More than a decade ago, Gusnard and Raichle (2001) proposed the default mode network (DMN) of the brain, which is tonically active and continuously gathering information about the world around and within us, thus enabling a continuous, stable and unified perspective of the organism relative to its environment. Key regions implicated in this network are the medial prefrontal cortex, the precuneus, and the posterior cingulate and retrosplenial cortex. At the same time, the precuneus and postcentral gyrus have been shown to be activated during imagination of one's own actions or movements and during tasks requiring introspection, self-evaluation and reflection upon one's own personality and mental state (Ruby and Decety, 2001; Farrer and Frith, 2002; Cavanna and Trimble, 2006). Ongoing research indicates that a core network, highly similar to the DMN, is engaged in diverse forms of self-projection, including episodic memory, prospection, theory of mind, and spatial navigation (Buckner and Carroll, 2007).

Up to now, structural and functional abnormalities of the precuneus, a key region of the DMN, have been frequently linked to mental disorders with core symptoms in the domain of identity and self-reflection, such as schizophrenia (e.g., Cooke et al., 2008; Morgan et al., 2010; Holt et al., 2011; Siemerkus et al., 2012), borderline personality disorder (e.g., Lange et al., 2005; Irle et al., 2007) and dissociative disorders (e.g., Simeon et al., 2000; Weniger et al., 2013). Three recent studies (Liao et al., 2010, 2011; Liu et al., 2013) found aberrant functional connectivity of the DMN in SAD, although there is a contrary report (Pannekoek et al., 2013). Structural abnormalities of the parietal cortices in SAD have also been reported recently (Syal et al., 2012; Talati et al., 2013; Brühl et al., 2014), but there are contrary reports as well (Liao et al., 2011; Frick et al., 2014).

The cognitive symptoms of SAD are described as an exaggerated negative self-reflection and self-focused attention, avoidance and safety behaviors, and anticipatory and post-event rumination (Clark and Wells, 1995). All these cognitive processes are likely to be associated with activity of the DMN, especially precuneus functioning, and abnormalities of brain regions in the DMN support shaping and

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maintaining symptoms of SAD. Accordingly, the goals of the present study were to investigate whether individuals with SAD show morphological abnormalities in the parietal cortices related to the DMN, and whether these parietal cortex abnormalities are related to the severity of SAD symptoms. Special emphasis was laid on the separate investigation of social anxiety and social avoidance, respectively, since the cognitive symptoms of SAD as described above relate to social avoidance. Furthermore, severe social avoidance has been shown to predict the persistence of SAD (Beesdo-Baum et al., 2012).

Participants comprised 67 persons with SAD and 64 matched healthy control subjects who underwent structural 3-Tesla three-dimensional magnetic resonance imaging (MRI) and a comprehensive clinical assessment. Voxel-based morphometry (VBM) was applied as a first-pass strategy to assess cortical abnormalities, and was used to detect possible structural abnormalities across the entire brain that were not initially hypothesized. As a second step, we performed manual segmentation of the parietal cortices. We used sulcal landmarks for the delineation of parietal cortex boundaries, as sulcal landmarks have the advantage of directly modeling the substantial interindividual morphological variability of the human cerebral cortex (Rademacher et al., 1992).

2. Methods

2.1. General procedures

Participants were recruited through advertisements or other information or were referred by psychotherapists or physicians in private practice. After complete description of the study to all participants, informed written consent was obtained. The Ethical Committee of the Medical Faculty of the University of Göttingen approved the study design.

2.1.1. Participants with SAD

The sample comprised 67 persons (32 males) with SAD according to the *Structured Clinical Interview for DSM-IV* (*SCID-I*) (Wittchen et al., 1997) (Table 1). Inclusion criteria for all participants were age 18–70 years, a score >30 on the *Liebowitz Social Anxiety Scale* (*LSAS*) (Mennin et al., 2002), and a primary diagnosis of SAD according to the rating on the *Anxiety Disorders Interview Schedule* (Brown et al., 1994). Participants with SAD and isolated performance anxiety were excluded, as there is evidence that this form of SAD has a favorable clinical course (Beesdo-Baum et al., 2012) and may represent a biologically different clinical entity (Stein et al., 2000). Furthermore, participants with a history of neurological disease, severe medical conditions, psychotic disorders, substance-related disorders, post-traumatic stress disorder, or personality disorders except for avoidant personality disorder (APD) (*SCID-II*) were excluded. Six participants were on antidepressant medication (escitalopram: two cases; sertraline: one case; paroxetine: one case; venlafaxine: one case; amitriptyline: one case). Twenty-four participants were included in a previous publication on hippocampal and amygdala size in SAD (Irle et al., 2010).

We assessed further clinical symptoms with the *State-Trait Anxiety Inventory* (*STAI*) (Spielberger et al., 1970) and the *Harm Avoidance* (*HA*) Scales of the *Tridimensional Personality Questionnaire* (*TPQ*) (Cloninger et al., 1999). Depressive symptoms were assessed with the *Beck Depression Inventory* (*BDI*) (Beck et al., 1960).

2.1.2. Healthy controls

Participants with SAD were compared with 64 healthy controls matched for sex, age and years of education (Table 1). Only participants without a history of neurological or psychiatric disorder (as assessed by the *SCID*) were studied.

2.2. Image acquisition

Data were acquired using a 3-Tesla Siemens Magnetom Trio (Siemens, Erlangen, Germany). Parameters of the T_1-weighted three-dimensional (3-D) sequence (turbo fast low angle shot) at 1-mm isotropic resolution were as follows: echo

Table 1
Clinical and socio-demographic data of participants with SAD and controls.

Characteristic	Participants with SAD ($n=67$)	Healthy controls ($n=64$)	Statistic	P
Age, years [range]	31 ± 10 [19–66]	32 ± 10 [19–69]	$t(129)=0.69$	0.495
Education, years	14 ± 2	15 ± 2	$t(129)=0.98$	0.327
Sex, male : female, no.	32 : 35	33 : 31		0.728[a]
Handedness, right : left, no.	62 : 5	56 : 6		0.757[a,b]
Intracranial volume, ml	1562 ± 154	1547 ± 112	$t(129)=-0.62$	0.538
Total brain volume, ml	1260 ± 141	1235 ± 100	$t(129)=-1.14$	0.259
Age at disorder onset, years	16 ± 6			
Disorder duration, years	15 ± 9			
DSM-IV diagnoses[c], no. of participants				
SAD	67			
APD	19			
MDD[d]	16			
Dysthymia	5			
Specific phobia	7			
Panic disorder	5			
Agoraphobia	2			
Generalized anxiety disorder	1			
Liebowitz Social Anxiety Scale (*LSAS*)				
Anxiety	37 ± 11	5 ± 4	$t(105)=-17.34$	<0.001[e]
Avoidance	31 ± 10	9 ± 6	$t(105)=-12.71$	<0.001[e]
State Trait Anxiety Inventory (*STAI*)				
State anxiety score	43 ± 10			
Beck Depression Inventory (*BDI*)	16 ± 9	4 ± 4	$t(105)=-8.35$	<0.001[e]
Harm Avoidance (*HA*)[f]				
Anticipatory worry	7 ± 2			
Fear of uncertainty	6 ± 2			
Shyness with strangers	6 ± 1			
Fatigability and asthenia	6 ± 3			

Means and standard deviations are given if not mentioned otherwise.
DSM-IV=4th edition of the Diagnostic and Statistical Manual of Mental Disorders; APD=avoidant personality disorder; MDD=major depressive disorder.

[a] Fisher's exact test.
[b] Information for two control subjects is missing.
[c] Lifetime disorders: MDD, $n=3$; specific phobia, $n=3$; panic disorder, $n=2$; agoraphobia, $n=1$.
[d] Mild ($n=10$) or moderate ($n=6$) current/most recent episode.
[e] Information for 24 control subjects is missing.
[f] Information for two participants is missing.